

Anabolic steroids and male infertility: a comprehensive review

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For several decades, testosterone and its synthetic derivatives have been used with anabolic and androgenic purposes. Initially, these substances were restricted to professional bodybuilders, becoming gradually more popular among recreational power athletes. Currently, as many as 3 million anabolic-androgenic steroids (AAS) users have been reported in the United States, and considering its increasing prevalence, it has become an issue of major concern. Infertility is defined as the failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse, with male factor being present in up to 50% of all infertile couples. Several conditions may be related to male infertility. Substance abuse, including AAS, is commonly associated to transient or persistent impairment on male reproductive

What's known on the subject? and What does the study add?

The negative impact of AAS abuse on male fertility is well known by urologists. The secondary hypogonadotropic hypogonadism is often highlighted when AAS and fertility are being discussed. On the other hand, the patterns of use, mechanisms of action and direct effects over the testicle are usually overseen. The present study reviews the vast formal and "underground" culture of AAS, as well as their overall implications. Specific considerations about their impact on the male reproductive system are made, with special attention to the recent data on direct damage to the testicle. To our knowledge this kind of overview is absolutely unique, offering a distinguished set of information to the day-by-day urologists.

function, through different pathways. Herein, a brief overview on AAS, specially oriented to urologists, is offered. Steroids biochemistry, patterns of use, physiological and clinical issues are enlightened. A further review about fertility outcomes among male AAS abusers is also presented, including the classic reports on transient axial inhibition,

and the more recent experimental reports on structural and genetic sperm damage.

KEYWORDS

anabolic steroids, male infertility, hypogonadism

INTRODUCTION

Since its isolation and characterization in 1935, there have been further studies on testosterone which have led to the synthesis of numerous derivatives with properties different from the original molecule. These derivatives are called anabolic-androgenic steroids (AAS), or more commonly, anabolic steroids. Initially, these substances were restricted to professional athletes and bodybuilders, becoming gradually more popular among recreational and non-professional power athletes. It is currently estimated that there are as many as three million AAS users in the USA [1]. Interestingly, two thirds of US users are non-competitive bodybuilders, or even non-athletes, who use these substances for aesthetic purposes only [2]. In addition, steroids may be found in 'dietary supplements', which are supposed to be AAS-free [3]. International surveys recently

reported an overall steroid contamination rate of 15–25%, depending on the country, and the increasing prevalence of AAS abuse is of major concern.

Infertility is defined as the failure to achieve a successful pregnancy after 12 months or more of regular unprotected intercourse, and male-factor infertility is the cause in ≈50% of all infertile couples. Several conditions may explain male-factor infertility. Some are identifiable, but not reversible; others may be identified and also reversed. Hypogonadotropic hypogonadism is a typical example of a reversible condition, whereas primary testicular impairment is often related to a less reversible one.

In the present paper we give a brief overview of AASs, with particular emphasis on urologists, enlightening steroids biochemistry, patterns of use and

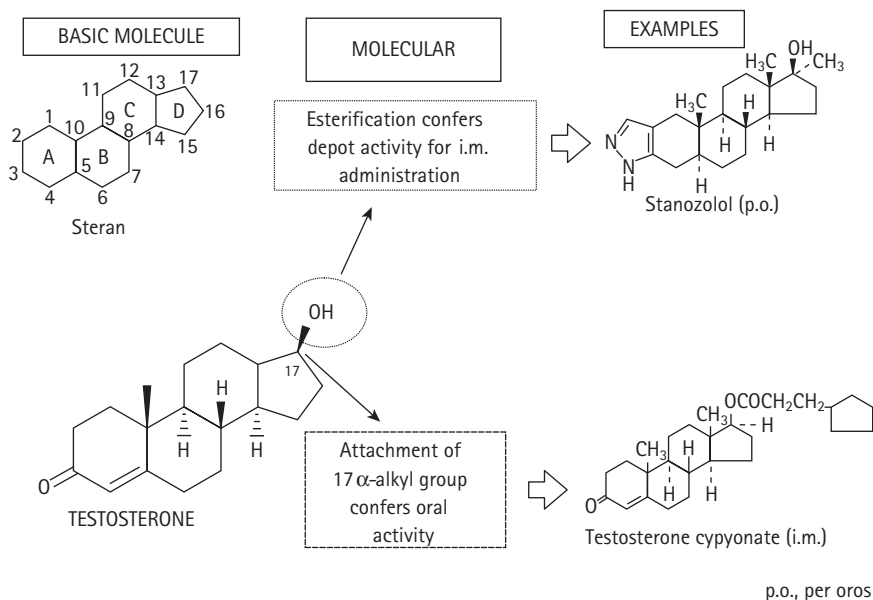
physiological and clinical issues. We also review fertility outcomes among male AAS abusers, including the classic reports on transient axial inhibition, and the more recent experimental reports on structural and genetic sperm damage.

ANABOLIC STEROIDS: WHAT DOES THE UROLOGIST NEED TO KNOW?

TESTOSTERONE FACTS

Testosterone is the most important androgen in the human body. The effects of androgens are most evident during puberty, as they elicit dramatic physiological changes in the male body, including the onset of secondary male characteristics, hair growth pattern, sebaceous gland activity and maturation of sperm and libido. These are considered the virilizing or 'androgenic' effects. Daily testosterone synthesis ranges from 2.1 to

FIG. 1. The basic 'steran nucleus', typical structural modifications and examples of modified molecules.



11.0 mg in individual males, with normal plasmatic levels of 300–1000 ng/dL, which progressively decline with age. Testosterone has several possible metabolic fates [4]. First, it binds to the androgen receptor (AR) in target tissues to exert its effects. Second, it is reduced to 5α-dihydrotestosterone (5DHT), which also acts on the AR. Following a different path, testosterone may be aromatized to oestradiol to exert oestrogenic effects, typically water retention, breast tissue growth and an increase in body fat deposition.

ANABOLISM VS. ANDROGENISM

Along with the androgenic changes comes the 'anabolic' effect. Anabolism is defined as any state in which nitrogen is differentially retained in lean body mass through the stimulation of protein synthesis and/or a reduction in protein breakdown [5]. It includes growth promotion, protein and collagen synthesis and an increase in muscle size and bone metabolism. Characteristically, steroids that are more anabolic present weaker AR bindings, and those that are more androgenic strongly bind the AR, exerting a more potent effect. A 'myotrophic-androgenic index', based on the association between anabolic and androgenic bioassays in rats has been previously described [4]. Although these assays were subject to several criticisms because of their unsophisticated *in vivo* nature, the activity of

many substances was assessed, allowing comparison between different substances. Since testosterone is the basic AAS, it has a 1:1 anabolic-androgenic ratio.

ANABOLIC STEROIDS: BEYOND TESTOSTERONE

Structural modifications have been made to the testosterone molecule in an attempt to maximize the anabolic effects and minimize the androgenic ones; however, all AASs are virilizing if administered for long enough, at high enough dosages [7]. AASs therefore include synthetic derivatives of testosterone, and not only testosterone itself. The AAS structural base is the 'steran nucleus'[4], consisting of three condensed cyclohexan rings, in nonlinear junction, and a cyclopentane ring (Fig. 1). The anabolic effects are dose-dependent, and usually occur when supraphysiological testosterone levels (>1000 ng/dL) are found, which generally requires weekly doses of 300 mg or more.

Traditionally, AASs are classified according to the route of administration and their carrier solvent and fall into two categories:

1. *Oral AASs or 17α-alkylated steroids.* The 17α-alkylated AAS group originate from the substitution of the 17α-hydrogen on the steroid nucleus for a methyl or ethyl group. Alkyl substitution prevents deactivation of the steroid by hepatic first-pass metabolism (necessitating hepatic monitoring), which

promotes oral activity. They usually have short half-lives, making several daily doses necessary to maintain appropriate blood levels. This class includes the very common stanozolol and oxandrolone, as well as methyltestosterone and others.

2. *Parenteral AAS or 17β-esterified steroids.* Usually the 17β-hydroxyl group is oesterified with an acid moiety to prevent rapid release from the oily vehicle. Roughly, the longer the chain length of the acid moiety, the more slowly the preparation is released into the blood stream. Once in the circulation, hydrolysis rapidly occurs yielding the active compound. They usually have a longer half-life and a slower absorption rate, bringing much less hepatic stress than the orally taken steroids. Pain at injection sites is common, because of the oily base. There are four basic active compounds: i) testosterone, bound to esters such as undecanoate, cypionate, propionate and others; ii) 19-nortestosterone (or nandrolone), also bound to different esters. Nandrolone is extremely popular, owing to its high anabolic : androgenic ratio. In contrast to testosterone, nandrolone is converted to a less potent metabolite after 5α-reduction. This, in addition to nandrolone's lesser affinity to AR, explains the higher myotrophic : androgenic ratio; iii) boldenone, bound to ester undecylenate; and iv) trenbolone, bound to ester acetate.

Anabolic-androgenic steroids may also be classified according to their main effects (Table 1). The main effects are as follows:

'Testosterone-like' effect. The testosterone-like effect is very potent, and allows great muscle strength gains. These AASs usually show an anabolic : androgenic ratio close to 1:1, similar to testosterone itself. The high aromatization rates are also comparable with those of testosterone. They include all testosterone esters, methyltestosterone and others.

'Dihydrotestosterone (DHT)-like' effect. The DHT-like effect is potent but highly androgenic. As these AASs resemble a 5DHT molecule, they cannot be aromatized to oestrogen and they also have a low water and salt retention. These AASs include stanozolol and oxandrolone.

'Nandrolone-like' effect. The nandrolone-like effect is the least potent of all, with the

highest anabolic : androgenic ratio. The AASs in this group have some progesterone-like activity, inhibiting the hypothalamic axis. These AASs are the most frequently used drugs in the clinical setting, when anabolic effects are desired (they reverse catabolic states, such as AIDS-associated cachexia, severe burns, and chronic obstructive pulmonary disease). They include the nandrolone esters and trembolone.

'STACKING' AND 'CYCLING'

Information about non-medical use of AASs is sparse. Several studies have looked at the unsupervised drug habits of AAS users, but these are clearly subject to different types of bias. Nevertheless, these field studies should not be overlooked. According to the studies, drug regimens follow typical patterns. Different oral and injectable compounds are generally combined ('stacked'), creating large-dose regimens usually self-administered during periods ('cycles') lasting 4–12 weeks [6]. 'Stacking' is based on the idea that smaller dosages of multiple drugs might reduce the chance of complications than larger dosages of a single drug. This may also facilitate the administration of multiple AASs (necessary to achieve supraphysiological doses) for longer periods, and so minimizing the plateauing effect. The aim of 'stacking' is to rationally combine different characteristics, avoiding overlap of benefits or side effects. Combinations of testosterone and nandrolone (or similar drugs) are the basis of the 'mass-building stacks', used to maximize muscular and strength gains. Combinations containing potent androgens are preferred for dieting and body definition, because of their lack of oestrogenic activity (less water, salt and fat retention). These are the 'cutting stacks'. Heavy users may combine a 'mass-building cycle' with a subsequent 'cutting cycle', finishing with a 'post-cycle therapy', with anti-oestrogens or hCG, in an attempt to restart androgen production. Frequent users may also combine AASs with other 'performance drugs', such as painkillers (including opioids), diuretics, insulin, growth hormone, stimulants, aromatase inhibitors and thyroxine.

PHYSIOLOGICAL AND CLINICAL EFFECTS AND SIDE EFFECTS

The physiological direct effects of testosterone and AASs (AR-mediated) are well known. They include increases in renal

TABLE 1 Commonest AASs in use worldwide, according to main effect

Compound name	Brand name
Testosterone-like effect	
Testosterone esters: cypionate	Deposteron®, Testex Leo®
Testosterone esters: undecanoate	Nebido®, Androxon®
Testosterone esters: blends	Durateston®, Testoviron®, Sustanon®, Omnadren®
Methyltestosterone	Methyltestosterone®, Metandren®
Methandrostenolone	Dianabol®, Anabol®, Naposim®
Chlorodehydromethyltestosterone	Turinabol®
Fluoxymesterone	Halotestin®
Boldenone	Equipoise®, Equilon®
DHT-like effect	
Stanozolol	Winstrol®, Stromba®
Oxandrolone	Anavar®
Oxymetholone	Anadrol®, Hemogenin®, Anapolon®
Mesterolone	Proviron®
Methenolone	Primobolan®
Nandrolone-like effect	
Nandrolone decanoate	Decadurabolin®
Nandrolone phenylpropionate	Durabolin®
Trenbolone	Finaplix®, Parabolan®
Nandrolone undecanoate	Dynabolan®

erythropoiesis, lipolysis, protein synthesis, sebaceous secretion, hair growth and libido [7]. However, the indirect effects should also be considered. These include anti-glucocorticoid effects, which are mediated by testosterone occupation of cortisol receptors (which have a remarkable affinity with testosterone) and create an anti-catabolic effect. An increase in muscular activity is certainly the leading result of AAS use. It constitutes a complex phenomenon involving hypertrophy of skeletal muscle fibres that contain muscle cells and undifferentiated satellite cells. The latter become myoblasts that are incorporated into skeletal muscle cells, increasing the number of nuclei, and also the amount of cytoplasm, actin and myosin, making them larger and more potent. Notably, this phenomenon does not increase the number of fibres, only their size.

Side effects of AASs are also well known [7]. Their incidence is unclear, as the denominator of AAS use is not clear. Acne, alopecia and LUTS attributable to prostate enlargement are usually related to the strong androgenic 5DHT-effect. Erectile dysfunction and libido loss may also occur, especially after discontinuation, when endogenous testosterone levels are usually low. A sustained increase in testosterone levels during 'cycles' leads to higher aromatization

rates of testosterone, which accounts for the gynaecomastia typically found in steroid users. Hepatic effects are most often related to oral alkylated agents. They include the uncommon hepatic peliosis, cholestatic jaundice and hepatic neoplasms, such as focal nodular hyperplasia, which are all closely related to dose and duration of usage. Hepatocellular carcinoma and Wilm's tumour are serious and rare side effects that are always related to long-term and heavy use. Interestingly, there are no reports linking AASs to prostate cancer or significant increases in PSA levels. The most severe consequences of long-term AAS use are associated with the cardiovascular system. Hypertension, arrhythmia, erythrocytosis and ventricular dysfunctions have been reported. Mortality risk among chronic users is estimated to be 4.6 times higher than among non-users. Cases of renal failure secondary to rhabdomyolysis and diffuse membranoproliferative glomerulonephritis in heavy users have been reported. Aggressive behaviour, depression, mood swings, altered libido, euphoria and even psychosis are some of the psychiatric patterns related to AAS. Overpharmacy may increase the risk of violent criminality. Withdrawal syndrome and dependency were also described, and the likelihood of psychiatric effects is greater where there is previous psychiatric history, or alcohol or drug abuse.

THE IMPACT OF ANABOLIC STEROIDS ON MALE INFERTILITY: WHAT DOES THE LITERATURE TELL US?

CLASSIC REVERSIBLE AAS-INDUCED HYPOGONADOTROPIC HYPOGONADISM

Infertility after AAS abuse commonly presents as oligozoospermia or azoospermia, associated with abnormalities in sperm motility and morphology [8]. According to most reports, sperm quality tends to recover spontaneously within 4–12 months after discontinuation [9]. However, the negative effect on semen quality may persist for longer periods. A hypogonadotropic hypogonadism state is induced, characterized by decreased serum testosterone concentrations, testicular atrophy and impaired spermatogenesis [10]. These effects result from the negative feedback of androgens on the hypothalamic-pituitary axis, and possibly from local suppressive effects of exogenous androgens on the testis. FSH and luteinizing hormone (LH) concentrations are typically low. In addition, during AAS use, serum androgen concentrations may be supraphysiologically high, but the hypogonadotropic state lowers the intratesticular testosterone concentrations required to maintain normal spermatogenesis. The management of AAS-induced male infertility has also been extensively reported. Simple discontinuation of AAS use may lead to fertility recovery in a certain proportion of male users [10], but there is little literature and considerable disagreement regarding the management of such cases. Patients may also be actively treated, in a manner similar to that used for other forms of hypogonadotropic hypogonadism infertility, requiring the induction of spermatogenesis with gonadotropins or gonadotropin analogues, including i.m. injections of hCG, human menopausal gonadotropin (hMG) or even recombinant FSH. The use of hCG alone, or in combination with hMG, has been reported to be a successful treatment for this group of patients [11]. Fertility restoration has been reported, even in situations of persistent azoospermia up to 5 years after AAS discontinuation so AAS-associated male infertility may be treatable because of its endocrine nature. Considering the prevalence of AAS abuse and the favourable results after treatment, it is reasonable to consider it during the infertility consultation.

INNOVATIVE EXPERIMENTAL AAS-INDUCED FINDINGS

Histopathology

Experiments in animal models mainly report AAS-induced Leydig cell alterations, but cellular morphology anomalies have also been reported [12]. The decrease in this population of cells is accompanied by low testosterone and LH levels in all papers reviewed, especially in those papers reporting on adult animal models. Immunohistochemical findings have suggested decreased steroidogenesis in testicular tissue, hence spermatogenesis was considered unchanged by some other authors. Nevertheless, specific end-stage spermatogenesis impairment, with a lack of advanced forms of spermatids, has been described [13]. After AAS discontinuation, Leydig cells tend to proliferate but remain below the regular counts, even after longer periods [14]. Clearly, long-lasting, or possibly persistent effects of AAS use cannot be ruled out.

Impact on semen quality

The use of a combination of hCG and steroids is a common practice among AAS users. The goal is to avoid the impact of LH suppression after long-term AAS administration, which may lead to a persistent state of hypogonadism and low-quality semen. Restoration of spermatogenesis has been described; however more abnormal and hypokinetic spermatozoa are found, even after hCG 'post-cycle' use, showing a potential for persistent alterations after the discontinuation of AAS use [15].

Apoptosis

Apoptosis has been reported to play an important role in the regulation of germ cell populations in the adult testis. Recently, the correlation between apoptosis and high AAS doses and exercises has been experimentally assessed in animal models. Shokri *et al.* report a significant increase in the rate of apoptosis after nandrolone administration, an increase clearly amplified by physical exercise [16]. Shokri *et al.* also report an evident impairment in semen quality among the same set of individuals, in the same conditions. Testicular histopathological evaluation according to Johnsen's method [17] has also been performed, revealing low quality spermatogenesis.

Aneuploidies and ultrastructural changes in spermatozoa

The innovative use of both transmission electron microscopy and fluorescence *in situ* hybridization (FISH) has recently been reported in an AAS user sperm sample, searching for genetic and ultrastructural consequences of steroid abuse. Immaturity, necrosis and apoptosis were assessed, and a high percentage of structurally normal spermatozoa were found, which showed the absence of a correlation between AAS and ultrastructural sperm changes. In contrast to these findings, FISH sperm analysis revealed XY and chromosomes 1 and 9 disomies, suggesting anomalies in the meiotic process and genetic damage among AAS users [18].

An overview of the effects of AAS use on male fertility is presented in Table 2 [9–18].

CONCLUSION

The common factor in the available medical literature on AAS misuse is a lack of homogeneity, not only in the subjects themselves, but also in the pattern of use of these substances. This prevents objective comparisons between drugs and regimens. AAS abuse may interfere in one's health in many ways. The impact on male fertility is one of the least reported, but certainly one that the urologist should know better, since a reversal of the majority of the dysfunctions caused can frequently be achieved, especially among non-heavy users. Correct medical orientation, identification of users and prompt clinical management of deleterious consequences are the cornerstone of good urological practice in these situations. There should be a physical examination and seminal analysis, and the hormone profile should be assessed. Immediate discontinuation should be encouraged. Attention should be paid to 'steroid-free' dietary supplements as, in some countries, up to 25% of these may contain traces of hormones. Most of the series reviewed show recovery of seminal and hormonal levels in periods of ≈6 months. When this is not achieved, testicular function may be boosted with gonadotrophin administration. Additionally, experimental studies and clinical series suggest some degree of gonadal impairment, which should lead us to conclude that the impact of steroids on male fertility is not solely a transient condition. As far as we can see, the

TABLE 2 Overview of effects of AASs on male fertility

Effect analysed	Reference	Study design	Outcome
Drug-induced hypogonadotropic hypogonadism (HH)	Turek <i>et al.</i> 1995 [9]	Case report	Complete reversion of persistent azoospermia after hCG treatment (2000–3000 IU three times a week for 4 months). It is recommended that therapy be started after a 6-month period of unsuccessful conservative management. Pregnancy was achieved after treatment.
	Gazvani <i>et al.</i> 1997 [10]	Case report	Four cases of AAS-induced HH and azoospermia were managed in a conservative fashion. Hormonal and seminal parameters were restored and 3/4 achieved pregnancy. Up to 10 months were required for restoration of semen quality.
	Menon 2003 [11]	Case report	AAS-induced azoospermia (persistent after 1 year of discontinuation of steroid use) was reversed with hCG (10 000 UI twice a week) and hMG (75 UI daily) for 3 months. Pregnancy was achieved.
Semen quality	Karila <i>et al.</i> 2004 [15]	Retrospective series	A total of 18 subjects were evaluated after AAS + hCG use. Transient HH was shown, with severe oligozoospermia. hCG therapy could restore spermatogenesis, but was positively correlated with morphological abnormalities in sperm after treatment.
Sperm apoptosis	Shokri <i>et al.</i> 2009 [16]	Experimental	Caspase-3 assay and terminal deoxynucleotidyl transferase enzyme-mediated dUTP nick end labelling were used to assess germ cell apoptosis after AAS therapy, and it was found to be significantly high. A decrease in germ cell layers and in semen quality were also found.
Testicular histology	Feinberg <i>et al.</i> 1996 [12]	Experimental	Leydig cell depletion and irregularly shaped Leydig cells were found during AAS administration. After discontinuation, Leydig cells increased in number, staying below the baseline even after long periods.
	Grockett <i>et al.</i> 1992 [13]	Experimental	End-stage spermatogenesis impairment resulted from AAS therapy; the most advanced stages of spermatids and mature sperm were lacking.
	Nagata <i>et al.</i> 1999 [14]	Experimental	Leydig cell depletion and arrest of advanced spermatogenesis were found. Immunopositive cells for inhibin and steroidogenesis enzymes decreased in the testicular interstitial compartment.
Sperm aneuploidies and meiotic segregation	Moretti <i>et al.</i> 2007 [18]	Case report	The FISH technique was used after spermatogenesis recovery, resulting in a higher frequency of XY disomy (segregation anomaly at the first meiotic division), and chromosomes 1 and 9 disomies.
Sperm ultra-structure	Moretti <i>et al.</i> 2007 [18]	Case report	After AAS discontinuation, spermatogenesis was induced with r-FSH (150 IU on alternate days) plus hCG (100 UI twice a week) for 6 months. Azoospermia was reversed and pregnancy was achieved. Sperm immaturity, necrosis and apoptosis were assessed through transmission electron microscopy. Ultra-structural sperm changes were not significantly high.

best policy is to strongly discourage steroid use, and to follow up those who persist with AAS abuse with suitable and ethical clinical and urological support.

CONFLICT OF INTEREST

None declared.

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Abbreviations: AAS, anabolic-androgenic steroid; AR, androgen receptor; DHT, dihydrotestosterone; 5DHT, 5 α -dihydrotestosterone; hMG, human menopausal gonadotropin; LH, luteinizing hormone; FISH, fluorescence *in situ* hybridization; HH, hypogonadotropic hypogonadism.